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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ISHLT CONSENSUS STATEMENTS

The management of antibodies in heart transplantation: An ISHLT consensus document

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KEYWORDS:
heart transplantation;
antibodies;
HLA;
sensitization;
crossmatch;
antibody-mediated rejection;
non-HLA antibodies

Despite the successes from refined peri-operative management techniques and immunosuppressive therapies, antibodies remain a serious cause of morbidity and mortality for patients both before and after heart transplantation. Patients awaiting transplant who possess antibodies against human leukocyte antigen are disadvantaged by having to wait longer to receive an organ from a suitably matched donor. The number of pre-sensitized patients has been increasing, a trend that is likely due to the increased use of mechanical circulatory support devices. Even patients who are not pre-sensitized can go on to produce donor-specific antibodies after transplant, which are associated with worse outcomes. The difficulty in managing antibodies is uncertainty over which antibodies are of clinical relevance, which patients to treat, and which treatments are most effective and safe. There is a distinct lack of data from prospective trials. An international consensus conference was organized and attended by 103 participants from 75 centers to debate contentious issues, determine the best practices, and formulate ideas for future research on antibodies. Prominent experts presented state-of-the-art talks on antibodies, which were followed by group discussions, and then, finally, a reconvened session to establish consensus where possible. Herein we address the discussion, consensus points, and research ideas.
J Heart Lung Transplant 2018;37:537–547

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The presence of circulating antibodies in heart transplantation (called sensitization) impacts clinical outcomes. Due to different clinical implications, sensitization can be

1053-2498/
https://doi.org/10.1016/j.healun.2018.01.1291

Table 1 Results of Pre-conference Online Survey[a]

On pre-transplant antibody detection:

- Asked which antibody test(s) were done pre-transplantation for patients with detected antibodies but who were not highly sensitized: 86% did a virtual crossmatch; 30% did a prospective flow cytometry; 32% did a prospective CDC crossmatch; 11% responded other; and 4% did none. (56/56 centers responded)
- The most frequently cited MFI cut-off for determining which corresponding antigens to avoid was 5,000, with a range from >0 to 10,000. (56/56)
- The frequency with which respondents monitored antibodies pre-transplant was: every 3 months for 34% of respondents; every 6 months for 19%; monthly for 15%; never if PRA was 0% at listing for 5%; with the remaining 27% of respondents varying the frequency based on waitlist status, PRA level, or for MCS patients. (56/56)
- 70% of respondents did not have a different approach for avoiding Class I vs Class II anti-HLA antibodies pre-transplant. (56/56)
- 56% of respondents routinely submitted unacceptable antibodies to their regulatory agency to use during the virtual crossmatch, and 44% did not. (55/56)
- Asked when the respondent would order a prospective crossmatch: 22% would do so for PRA >25%; 19% would never do so if the virtual crossmatch was negative; 8% would for PRA >80%; 5% would for PRA >70%; 5% would for PRA >50%; and 41% either always did one, did one for any sensitized patient, or used other factors such as the distance from the donor. (56/56)
- 48% of respondents would decline a donor heart if the flow cytometry crossmatch was positive, and 75% would decline if the CDC crossmatch was positive. (52/56)

On sensitized patients:

- 75% of respondents desensitized patients before transplantation, and 25% did not. (56/56)
- Asked which antibody detection method respondents used for deciding to initiate desensitization therapy: 62% used cPRA; 13% used general PRA; and 25% relied on other factors, such as an MFI cut-off, antibody specificity, CDC positivity after EDTA, complement levels, IgG/IgM levels, or the probability of transplantation. (52/56)
- When asked which PRA or cPRA values trigger desensitization therapy: 21% used >80%; 21% used >50%; and the remainder used values that ranged from >10% to >90%. Some centers combined MFI values, the frequency of positive crossmatches, blood group status, and the likelihood of being transplanted. (56/56)
- 48% of respondents believed that sensitized VAD patients posed the same risk as sensitized non-VAD patients; 29% thought sensitized VAD patients were less at risk; and 23% did not know. (56/56)
- The most commonly used treatments for desensitization therapy were IVIg, plasmapheresis, rituximab, and bortezomib. (54/46)
- 78% of respondents did not change their desensitization treatments for Class I vs Class II antibodies pre-transplant, and 22% did. (55/56)
- 73% of respondents used special treatments for sensitized patients peri-operatively and 27% did not. (56/56)
- Of the respondents who did use special treatments, the most commonly used therapies were ATG, plasmapheresis, and IVIg. (47/47)

On antibody treatment:

- 78% of respondents did not change their approach for treating Class I vs Class II DSA, and 22% did. (55/56)
- When asked, which therapy was first-line in the treatment of antibodies: 79% used IVIg; 62% used plasmapheresis; 52% used rituximab; 19% used ATG; 8% used bortezomib; and 17% used other therapies, including carfilzomib, MMF, cyclophosphamide, and immunoadsorption. (51/56)
- On the treatment of DSA, 69% of respondents would treat if there was cardiac dysfunction; 58% would treat with biopsy-proven AMR Grade 1 or 2; 15% would treat only with high-level DSA; 11% would treat for all cases; 11% would treat only if the DSA were $C1q^{+}$, and 2% did not treat DSA. (54/56)
- The most commonly used therapies for treating DSA were plasmapheresis, rituximab, IVIg, augmenting corticosteroids, ATG, and bortezomib. (54/56)
- The most commonly used first-line therapies for treating DSA were: plasmapheresis, IVIg, and rituximab. (54/56)
- Respondents were asked whether their approach to treating DSA differed <1 year post-transplantation vs >1 year transplantation: 65% did not change their approach, and 35% did. (55/56)
- 78% of respondents did not treat Class I vs Class II DSA post-transplant differently, and 22% did. (55/56)

On post-transplant antibody surveillance:

- 73% of respondents routinely monitored antibodies post-transplantation; 18% would only monitor antibodies if they were detected pre-transplant; and 9% would do so in patients with biopsy-proven AMR or PGD. (56/56)
- 80% of respondents monitored antibodies at 1, 3, 6, and 12 months post-transplantation; 28% also did so at 9 months; and a small minority did so every month in the first year. (50/56)
- After the first year post-transplantation, 41% of respondents monitored antibodies annually; 29% did not monitor at all; 20% did so on a for-cause basis; 14% did so every 6 months; and 6% did so every 3 months. (54/56)
- For DSA-positive patients, 35% of respondents checked if the DSA could fix complement, and 65% did not. (55/56)
- For patients with DSA, 52% of respondents would perform a biopsy if there was also cardiac dysfunction; 29% did so in all cases; 15% did so if the DSA level was high; 12% did not do a biopsy; and 9% did so only if the C1q was positive. (54/56)
- 67% of respondents did not view non-HLA antibodies as concerning, and 33% did. (55/56)
- Respondents who monitored for non-HLA antibodies looked at anti-MICA, anti-MICB, anti-AT1 receptor, anti-vimentin, and anti-endothelial antibodies. (21/21)

AMR, antibody-mediated rejection; AT1, angiotensin 1; ATG, anti-thymocyte globulin; CDC, complement-dependent cytotoxicity; cPRA, calculated panel-reactive antibody; DSA, donor-specific antibody/antibodies; EDTA, ethylene-diamine tetraacetic acid; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin; MCS, mechanical circulatory support; MFI, mean fluorescence intensity; MICA/B, MHC Class I polypeptide-related sequence A/B; MMF, mycophenolate mofetil; PGD, primary graft dysfunction; PRA, panel-reactive antibody; VAD, ventricular assist device.

[a]There were 56 participating centers.